

Amendments to the Specification:

Please replace paragraph [0001] with the following amended paragraph:

[0001] A portion of the work set forth herein was supported by grants NIHGMS-[48829] 48893 and NSF MCB-9406656 and by the Medical University of South Carolina..

Please replace paragraph [0007] with the following amended paragraph:

[0007] Methods of making relaxin are described in U.S. Pat. No. 4,835,251 and U.S. Pat. No. 5,464,756 (PCT US90/02085) and PCT US94/06997 ~~in co-pending U.S. Ser. Nos. 07/908,766 (PCT US90/02085) and 08/080,354 (PCT US94/06999)~~. Methods of using relaxin in cardiovascular therapy and in the treatment of neurodegenerative diseases are described in U.S. Pat. No. 5,166,191 and in ~~U.S. Ser. No. 07/902,637 (PCT US92/06927)~~ PCT US92/06927. Certain formulations of human relaxin are described in ~~allowed U.S. Ser. No. 08/050,745~~ U.S. Pat. No. 5,451,572.

Please replace paragraph [0018] with the following amended paragraph:

[0018] FIG. 1. FIG. 1 depicts the primary structure of the relaxin-like factor (SEQ ID NO:3 and SEQ ID NO:4), as compared with the sequences of human relaxin (SEQ ID NO:2 and SEQ ID NO:5) and insulin (SEQ ID NO:1 and SEQ ID NO:6) wherein the relative positions of the B-chain arginines in RLF, as compared to relaxin, is highlighted.

Please replace paragraph [0031] with the following amended paragraph:

[0031] The term "relaxin" means human relaxin, including full length relaxin or a portion of the relaxin molecule that retains biological activity [as described in U.S. Pat. No. 5,023,321, preferably recombinant human relaxin (H2)] and other active agents with relaxin-like activity, such as agents that competitively displace bound relaxin from a receptor. Relaxin can be made by any method known to those skilled in the art, preferably as described in U.S. Pat. No. 4,835,251 and in ~~co-pending U.S. Ser. Nos. 07/908,766~~ U.S. Pat. No. 5,464,756 (PCT US90/02085) and 08/080,354 (PCT US94/06999) PCT US94/06997.

Please replace paragraph [0033] with the following amended paragraph:

[0033] RLF shares primary and secondary structural homology with relaxin, insulin and the other members of the insulin-related family of hormones. As reported previously, RLF is structurally closer to insulin than relaxin. The deduced primary structure of RLF is set forth at FIG. 1 (SEQ ID NOS:3 and 4).

Please replace paragraph [0036] with the following amended paragraph:

[0036] The deduced amino acid sequence for RLF would have predicted an opposite result because the critical ~~Arg-XXX-Arg~~ two Arg residues separated by three amino acids sequence in RLF is offset toward the C-terminal end of the B chain by exactly one turn of the helix. Thus, although RLF projects the arginines at nearly right angles away from the molecular surface in the manner of relaxin, one would expect that shifting the whole receptor-binding site would present quite a different binding environment to the receptor.

Please replace paragraph [0042] with the following amended paragraph:

[0042] Importantly, it has been observed in human relaxin that the arginines at positions B13 and B17 and potentially the amino acids of the first helix turn in the midregion of the B-chain (Arg-Glu-Leu-Val-Arg) (amino acid residues 13 to 17 of SEQ ID NO:5) are necessary or important to relaxin activity. Other RLF analogs and derivatives may be obtained using known techniques and this structural information regarding relaxin.

Please replace paragraph [0047] with the following amended paragraph:

[0047] RLF may be produced using techniques previously disclosed as useful in producing relaxin and insulin. For example, the cDNA for RLF disclosed in Burkhardt, et al., 1994, Genomics 20:13-19 and Adham, et al., 1994, J. Biol. Chem. 268:26668-26672 may be used to recombinantly produce RLF according to processes previously described as useful in

recombinantly manufacturing relaxin (e.g., U.S. Pat. Nos. 4,758,516, 4,871,670, 4,835,251 and ~~co-pending U.S. Ser. Nos. 07/908,766~~ U.S. Pat. No. 5,464,756 (PCT US90/02085) and ~~08/080,354 (PCT US94/0699)~~ PCT US94/06997). Similarly, such sequence information may be used to synthesize RLF according to the methods of Bullesbach and Schwabe, 1991, J. Biol. Chem. 266:10754-10761, for synthesizing relaxin.

Please replace paragraph [0051] with the following amended paragraph:

[0051] Relaxin may also be synthesized according to the techniques described above, with respect to RLF, or alternatively, recombinantly, by relying upon the disclosed nucleic acid sequences and deduced amino acid sequences for relaxin. In humans, two gene forms encoding for human relaxin have been identified, (H1) and (H2) and their use to recombinantly manufacture relaxin, and preferably relaxin (H2), have been described. Hudson, et al., 1983, Nature 301 628-631; Hudson, et al., 1984, EMBO J., 3:2333-2339; and U.S. Pat. Nos. 4,758,516 and 4,871,670. Methods of making relaxin are also described in U.S. Pat. No. 4,835,251 and in ~~co-pending U.S. Ser. Nos. 07/908,766~~ U.S. Pat. No. 5,464,756 (PCT US90/02085) and ~~08/080,354 (PCT US94/0699)~~ PCT US94/06997.

Please replace paragraph [0055] with the following amended paragraph:

[0055] Relaxin has been implicated consequently in the treatment and diagnosis of various diseases and disorders. For example, studies provide evidence that relaxin is effective in the treatment of scleroderma, sinus bradycardia, cardiovascular disease, neurodegenerative and neurologic disorders, hair loss, depression. See e.g., U.S. Pat. No. 5,166,191; U.S. Ser. No. 07/902,637 (PCT US92/069); U.S. ~~Applications entitled "Method For Treatment Of Hair Loss" and "Method For Treatment Of Depression," both of which are~~ Ser. No. 08/483,474 filed concurrently herewith. Evidence also suggests the use of relaxin in diseases and disorders related to the abnormal expression of collagen or fibronectin, such as scleroderma or rheumatoid arthritis.

Please replace paragraph [0057] with the following amended paragraph:

[0057] Additionally, as more fully discussed in the U.S. Application entitled "Relaxin Diagnostic Assays and Kits," filed concurrently herewith on June 7, 1995, U.S. Serial No. 08/488,399, diagnostic assays for determining the predisposition or presence of prostate, breast, testicular, ovarian and other cancers having common stem cell heritage, which rely on detecting the presence of relaxin may also be adjusted to rely upon the detection of RLF. Such assays can also be used to follow-up on tumor metastases after ablation of cancer.

Please replace paragraph [0092] with the following amended paragraph:

[0092] RLF for treatment of such disorders such as alopecia, may also be administered topically in a formulation adapted for application to the scalp, such as a shampoo (e.g., as disclosed in U.S. Pat. No. 4,938,953, adapted according to methods known by those skilled in the art, as necessary for the inclusion of protein ingredients) or a gel (e.g., as disclosed in ~~allowed U.S. Ser. No. 08/050,745~~ U.S. Pat. No. 5,451,572) optionally with increased relaxin concentrations to facilitate absorption.

Please replace paragraph [0099] with the following amended paragraph:

[0099] More specific dosage, formulation and methods of administration may be derived from information contained in U.S. Pat. No. 5,166,191, ~~U.S. application Ser. Nos. 07/902,637 (PCT US92/06927) and 08/050,745 (allowed)~~, PCT US92/06927 and U.S. Pat. No. 5,451,572 and co-pending applications, filed concurrently herewith ~~entitled "Method Of Treatment For Hair Loss" and "Method Of Treatment For Depression."~~

Please replace paragraph [0137] with the following amended paragraph:

[0137] As discussed above, this result was surprising because the critical ~~Arg XXX Arg~~ sequence in RLF consisting of two Arg residues separated by three amino acids is offset toward the C-terminal end of the B chain by exactly one turn of the helix (See, FIG. 1).